JACC: CARDIOVASCULAR INTERVENTIONS
VOL. 8, NO. 13, 2015

ISSN 1936-8798/$36.00
PUBLISHED BY ELSEVIER INC.
http://dx.doi.org/10.1016/j.jcin.2015.07.021

PERIPHERAL

# Safety and Efficacy of Stent Retrievers for the Management of Acute Ischemic Stroke

## Comprehensive Review and Meta-Analysis

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**CME Objective for This Article:** At the completion of this article, the learner should be able to: evaluate the safety and efficacy of stent retriever for the management of acute ischemic stroke.

**CME Editor Disclosure:** *JACC: Cardiovascular Interventions* CME Editor Olivia Hung, MD, PhD, has received research grant support from NIH T32, Gilead Sciences, and Medtronic Inc.

**Author Disclosures:** The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

#### CME Term of Approval

Issue Date: November 2015
Expiration Date: October 31, 2016

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Manuscript received May 11, 2015; revised manuscript received June 23, 2015, accepted July 17, 2015.

# Safety and Efficacy of Stent Retrievers for the Management of Acute Ischemic Stroke

## Comprehensive Review and Meta-Analysis

**ABSTRACT**

**OBJECTIVES** This study sought to evaluate the safety and efficacy of stent retriever for the management of acute ischemic stroke.

**BACKGROUND** Stroke is the third leading cause of death and the most common cause of disability in the United States. Early reperfusion has been associated with favorable outcomes. Stent retrievers are novel endovascular devices that provide vessel recanalization via thrombus retrieval mechanical thrombectomy.

**METHODS** The authors performed a literature search using PubMed, EMBASE, and Cochrane Central Register of Controlled Trials from May 2005 to May 2015. Randomized controlled trails (RCTs) comparing endovascular therapy (ET) with the use of retrievable stents against standard therapy (ST) for the management of acute stroke were included.

**RESULTS** Five RCTs (the MR CLEAN, ESCAPE, EXTEND-IA, SWIFT-PRIME, and REVASCAT studies) with 634 patients in the ET group and 653 patients in the ST group met inclusion criteria. The frequency of a low 90-day modified Rankin Score (0 to 2) in the intervention group was 42.6% compared with 26.1% in the control group (odds ratio: 2.43; 95% confidence interval [CI]: 1.9 to 3.09; $p < 0.0001$). The frequency of intracranial bleeding was 4.2% in the ET group compared with 4.3% in the ST group (risk ratio: 1.08; 95% CI: 0.64 to 1.82; $p = 0.78$). 90-day mortality was 15.1% in the ET group compared with 18.7% in the ST group (risk ratio: 0.81; 95% CI: 0.58 to 1.12; $p = 0.19$). There was no evidence of significant heterogeneity or publication bias for any of the endpoints.

**CONCLUSIONS** On the basis of the results of this meta-analysis of RCTs, ET with stent retrievers appears as a safe and effective therapeutic option for acute ischemic stroke due to large vessel occlusion. (J Am Coll Cardiol Intv 2015;8:1758–65)


Stroke is the third leading cause of death and the most common cause of disability in the United States (1). For acute ischemic stroke, early reperfusion has been associated with favorable outcomes (2). To date, intravenous thrombolysis within 4.5 h after the onset of acute stroke symptoms is the most widely accepted strategy for prompt recanalization (3). However, the narrow time window, the low recanalization rates in patients with large vessel occlusion and bleeding complications often limit its use (4). Catheter-based therapies such as thromboembolectomy, suction thrombectomy, angioplasty with stenting, and stent retriever thrombectomy have been tried in patients with acute ischemic stroke alone or combined with intravenous or intra-arterial thrombolysis with variable recanalization and clinical outcomes (5,6). The best endovascular method has not yet been reliably determined. Stent retrievers (or retrievable stents) are endovascular devices that provide vessel recanalization via thrombus-retrieval mechanical thrombectomy. They are deployed inside the clot in order to envelop it within the stent struts. Subsequently, the stent retriever with the entrapped thrombus is pulled out of the artery. This mechanism combines the high rates of prompt flow restoration with stenting and mechanical thrombectomy without the risks of in-stent restenosis and thrombosis with conventional stents (7). They have been successfully used in recent acute stroke randomized controlled trials (RCTs). In view of several recently published large RCTs, the present meta-analysis seeks to systematically analyze the available evidence to evaluate the safety and efficacy of stent retriever therapy for the management of acute ischemic stroke.

## METHODS

A protocol was prospectively developed that detailed the specific objectives, criteria for study selection, approach to assess study quality, outcomes, and

**ABBREVIATIONS AND ACRONYMS**

**IV** = intravenous

**NIHSS** = National Institute of Health Stroke Scale/Score

**RCT** = randomized controlled trial

**RR** = risk ratio

statistical methods. We performed a literature search using PubMed, EMBASE, Cochrane Central Register of Controlled Trials, and Internet-based sources of information on clinical trials (ClinicalTrials.gov) from May 2005 to May 2015. The Medical Subject Heading (MeSH) terms "endovascular therapy and ischemic stroke" and "intra-arterial therapy and ischemic stroke" and "randomized controlled trials" were used. No language restrictions were applied. Bibliographies of relevant studies and the "Related Articles" link in PubMed were used to identify additional studies. Published abstracts from the annual meetings of the American

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College of Cardiology, American Heart Association, European Society of Cardiology, Trans Catheter Therapeutics, Society of Coronary Angiography and Intervention, and Euro Percutaneous Coronary Revascularization, International Stroke Conference were also identified. RCTs comparing the use of retrievable stents with conventional therapy were included in the meta-analysis. The final search yielded 5 RCTs comparing stent retrievers with conventional management of acute stroke (8-12).

**DATA EXTRACTION.** Two investigators (K.M. and M.C.) independently reviewed the studies and reported the results in a structured dataset. Studies were evaluated carefully for duplicate or overlapping data. Disparities between investigators regarding the inclusion of each trial were resolved by consensus by a third independent investigator (C.I.). Eligible trials to be included in our meta-analysis had to meet the following criteria: RCTs that compared the use of endovascular therapy of acute stroke with the use of retrievable stents against conventional therapy. Prespecified data elements were extracted from each trial as follows: sample size, sex, age, baseline National Institute of Health Stroke Scale/Score (NIHSS), use of intravenous tissue plasminogen activator, history of diabetes and atrial fibrillation, 90-day modified Rankin Score 0 to 2, symptomatic intracranial hemorrhage, and 90-day mortality. Events from each trial were recorded according to the intention-to-treat principle. The primary endpoints were "functional independence" defined as low 90-day modified Rankin Score 0 to 2, symptomatic intracranial hemorrhage, and 90-day mortality.

**STATISTICAL ANALYSIS.** We used risk ratios (RRs) with 95% confidence intervals (CIs) as the metric of choice for all outcomes. Categorical variables were reported as percentages, and continuous variables as mean ± SD. Weighted means were used for the pooled estimates of continuous variables. The pooled RR was calculated with the DerSimonian-Laird method for random effects (13). For all the treatment effects that were statistically significant, we determined the absolute risk reduction or the absolute risk increase, and also the corresponding number needed to treat or number needed to harm. To assess heterogeneity across trials, we used the Cochran Q via a Mantel-Haenszel test based on the pooled RR. Heterogeneity was also assessed by means of the $I^2$ statistic as proposed by Higgins et al. (14) (determining the variance across groups as a result of heterogeneity instead of chance). Based on the $I^2$ statistic, values of 25%, 50%, and 75% were considered as yielding low, moderate, and high heterogeneity, respectively (13,15,16). Results were considered statistically significant at $p < 0.05$. A funnel plot and the adjusted rank correlation test were used to assess for publication bias with respect to the primary outcome of interest. With the use of a funnel plot, the RR was plotted on a logarithmic scale against its corresponding standard for each study. In the absence of publication bias, one would expect studies of all sizes to be scattered equally right and left of the line showing the pooled estimate of natural log RR. Begg's and the weighted regression test of Egger ($p < 0.05$) were also used to assess a publication bias (17). A post-hoc sensitivity analysis was planned in case of significant heterogeneity including studies with similar outcome measures and mean follow-up duration. Statistical analyses were performed with RevMan software version 5.2.0 (Cochrane's Informatics & Knowledge Management Department) and Comprehensive Meta-Analysis Software (Biostat, Englewood, New Jersey).

## RESULTS

Of the 1,988 citations found, 5 RCTs were identified. Characteristics of the 5 RCTs are summarized in **Table 1** and **Figure 1**. All RCT studies were multicenter. MR CLEAN (MR CLEAN: Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) and REVASCAT (Endovascular Revascularization With Solitaire Device Versus Best Medical Therapy in Anterior Circulation Stroke Within 8 Hours) were performed in a single country, EXTEND IA (Extending the Time for Thrombolysis in Emergency Neurological Deficits—Intra-Arterial) in 2 countries, and SWIFT-PRIME (Solitaire FR as Primary Treatment for Acute Ischemic Stroke) and ESCAPE (Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke) were international. MR CLEAN included the

**TABLE 1 Characteristics of the Randomized Controlled Trials**

| Study Name, Year | Location | n | Comparison | Primary Outcome | Use of Retrievable Stents |
|---|---|---|---|---|---|
| MR CLEAN, 2015 | Netherlands (16 centers) | 500 | Mechanical treatment, delivery of a thrombolytic agent, or both vs. conventional therapy | Modified Rankin Score at 90 days | 97% |
| SWIFT-PRIME, 2015 | International (90 centers) | 196 | IV t-PA + Solitaire vs. IV t-PA alone | Modified Rankin Score at 90 days | 100% |
| EXTEND-IA, 2015 | Australia and New Zealand (14 centers) | 70 | Endovascular thrombectomy with retrievable stent vs. conventional therapy | Reperfusion at 24 h<br>Early neurologic improvement (≥8-point reduction on the NIHSS or a score of 0 or 1) | 100% |
| ESCAPE, 2015 | International (44 centers) | 315 | Mechanical treatment vs. conventional therapy | Modified Rankin Score at 90 days | 86.1% |
| REVASCAT, 2015 | Spain (4 centers) | 206 | Endovascular thrombectomy with retrievable stent vs. conventional therapy | Modified Rankin Score at 90 days | 100% |

ESCAPE = Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke; EXTEND-IA = Extending the Time for Thrombolysis in Emergency Neurological Deficits-Intra-Arterial; IV = intravenous; MR CLEAN = MR CLEAN: Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; NIHSS = National Institute of Health Stroke Scale/Score; REVASCAT = Endovascular Revascularization With Solitaire Device Versus Best Medical Therapy in Anterior Circulation Stroke Within 8 Hours; SWIFT-PRIME = Solitaire FR as Primary Treatment for Acute Ischemic Stroke; t-PA = tissue plasminogen activator.

largest number of patients (500), followed by ESCAPE (315). The primary outcome was 90-day modified Rankin Score in MR CLEAN, SWIFT-PRIME, ESCAPE, and REVASCAT, whereas in EXTEND-IA, the primary outcome was reperfusion at 24 h and early neurological improvement (≥8-point reduction on the NIHSS or a score of 0 or 1). Three studies (SWIFT-PRIME, EXTEND-IA, and REVASCAT) used exclusively stent retrievers as their endovascular thrombectomy device, whereas MR CLEAN and ESCAPE used retrievable stents in the majority of cases (97% and 86.1%, respectively). The baseline age and sex characteristics were comparable in all trials. In the EXTEND-IA study, the baseline NIHSS Stroke Scale was significantly lower in the conservative group compared with the intervention group (13 vs. 16), whereas the percentage of diabetic patients was higher (23% vs. 6%). SWIFT-PRIME and ESCAPE included the higher number of patients with known atrial fibrillation (35% to 40%), whereas ESCAPE had the highest percentage of diabetic patients (>20%). The baseline characteristics are summarized in Table 2 and the clinical outcomes in Table 3.

**FUNCTIONAL OUTCOME.** Rates of 90-day modified Rankin Score were reported in all trials (Figure 2). The overall frequency of functional independence (a low 90-day modified Rankin Score 0 to 2) in the intervention group was 42.6% (293 of 634) compared with 26.1% (171 of 653) in the control group. Patients in the intervention group had an odds ratio of 2.43 (95% confidence interval: 1.91 to 3.09; $p < 0.0001$) for having a modified Ranking Score of 0 to 2 compared with conventional therapy group. There was no evidence of statistical heterogeneity among studies ($I^2 = 0\%$; heterogeneity $p = 0.94$) (number needed to treat = 6.25 patients). There was no evidence of publication bias for this endpoint both on visual estimation of the funnel plot and on Egger's regression analysis ($p = 0.4$).

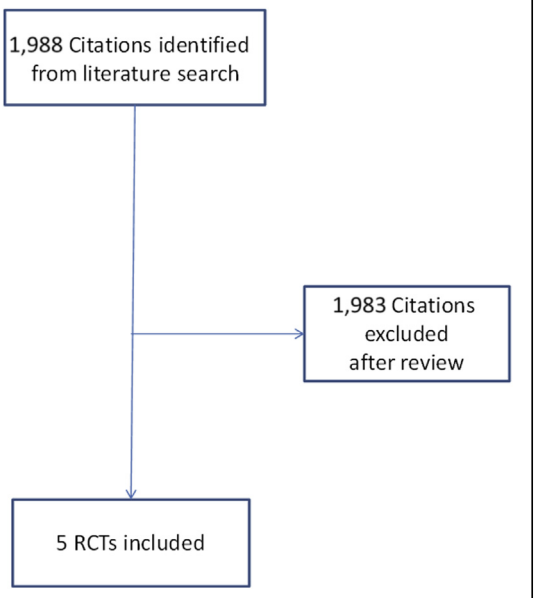
**INTRACRANIAL HEMORRHAGE.** Rates of intracranial bleeding were reported in all 5 trials. The overall frequency of intracranial bleeding was 4.2% in the intervention group (27 of 634) compared with 4.3% in the control group (28 of 652). The RR for intracranial bleeding 1.08 (95% CI: 0.64 to 1.82; $p = 0.78$). There was no evidence of statistical heterogeneity among studies ($I^2 = 0\%$; heterogeneity $p = 0.63$).

**NINETY-DAY MORTALITY.** Ninety-day mortality (Modified Rankin Score 6) was reported in all trials. The overall 90-day mortality was 15.1% in the intervention group (96 of 634) compared with 18.7% in the control group (122 of 653). The RR for 90-day mortality was 0.81 (95% CI: 0.58 to 1.12; $p = 0.19$) showing a trend towards lower 90-day mortality that was not statistically significant. There was no evidence of significant statistical heterogeneity among studies ($I^2 = 29\%$; heterogeneity $p = 0.23$).

## DISCUSSION

This meta-analysis of 5 most recent RCTs (MR CLEAN, ESCAPE, EXTEND-IA, SWIFT-PRIME, and REVASCAT) evaluating the addition of endovascular treatment of ischemic stroke related to proximal intracranial

**FIGURE 1 Meta-Analysis Flow Diagram**




RCT = randomized controlled trial.

arterial occlusion to conventional therapy (including intravenous [IV] thrombolysis) demonstrates the efficacy of endovascular treatment in improving functional outcomes and remarkable safety as demonstrated by no difference in rates of symptomatic intracranial hemorrhage compared with standard therapy. Furthermore, there appears to be a trend towards overall decreased 90-day mortality. The infrequent convergence of 5 positive RCTs, even after taking their differences into account, leads to the apparently uncontestable assertion that there is no longer equipoise in endovascular treatment of ischemic stroke (18).

Similar outcomes were noted between the 4 studies that used some form of neuroimaging selection (mismatch or core-infarct volume), compared to the fifth one (MR CLEAN study) that only required demonstration of vessel occlusion. This solidifies the dictum that "time is brain": endovascular treatment is effective at the early stages of cerebral ischemia due to large-vessel occlusion, whereas imaging selection may identify patients with ischemic injury that progresses slowly, and may thus be candidates for treatment at extended time points. This was also confirmed in the DEFUSE-2 study (Diffusion Weighted Imaging Evaluation for Understanding Stroke Evolution Study-2) in which it was noted that certain patients may have a slower rate of

**TABLE 2 Baseline Characteristics of the Randomized Controlled Trials**

| Study Name, Year | Number of Patients | | Male, % | | Age, yrs | | NIHSS Score | | IV Thrombolysis, % | | Diabetes, % | | Atrial Fibrillation, % | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Intervention | Control | Intervention | Control | Intervention | Control | Intervention | Control | Intervention | Control | Intervention | Control | Intervention | Control |
| MR CLEAN, 2015 | 233 | 267 | 57.9 | 58.8 | 65.8 | 65.7 | 17 | 18 | 87.1 | 90.6 | 14.6 | 12.7 | 28.3 | 25.8 |
| SWIFT-PRIME, 2015 | 98 | 98 | 55.1 | 46.9 | 65 | 66.3 | 17 | 17 | 100.0 | 100.0 | 12.2 | 15.5 | 35.7 | 39.2 |
| EXTEND-IA, 2015 | 35 | 35 | 49.0 | 49.0 | 68.6 | 70.2 | 17 | 13 | 100.0 | 100.0 | 6.0 | 23.0 | 34.0 | 31.0 |
| ESCAPE, 2015 | 165 | 150 | 47.9 | 47.3 | 71 | 70 | 16 | 17 | 72.7 | 78.7 | 20.0 | 26.0 | 37.0 | 40.0 |
| REVASCAT, 2015 | 103 | 103 | 53.4 | 52.4 | 65.7 | 67.2 | 17 | 17 | 68.0 | 77.7 | 21.4 | 18.4 | 34.0 | 35.9 |

Abbreviations as in Table 1.

**TABLE 3 Clinical Outcomes of the Randomized Controlled Trials**

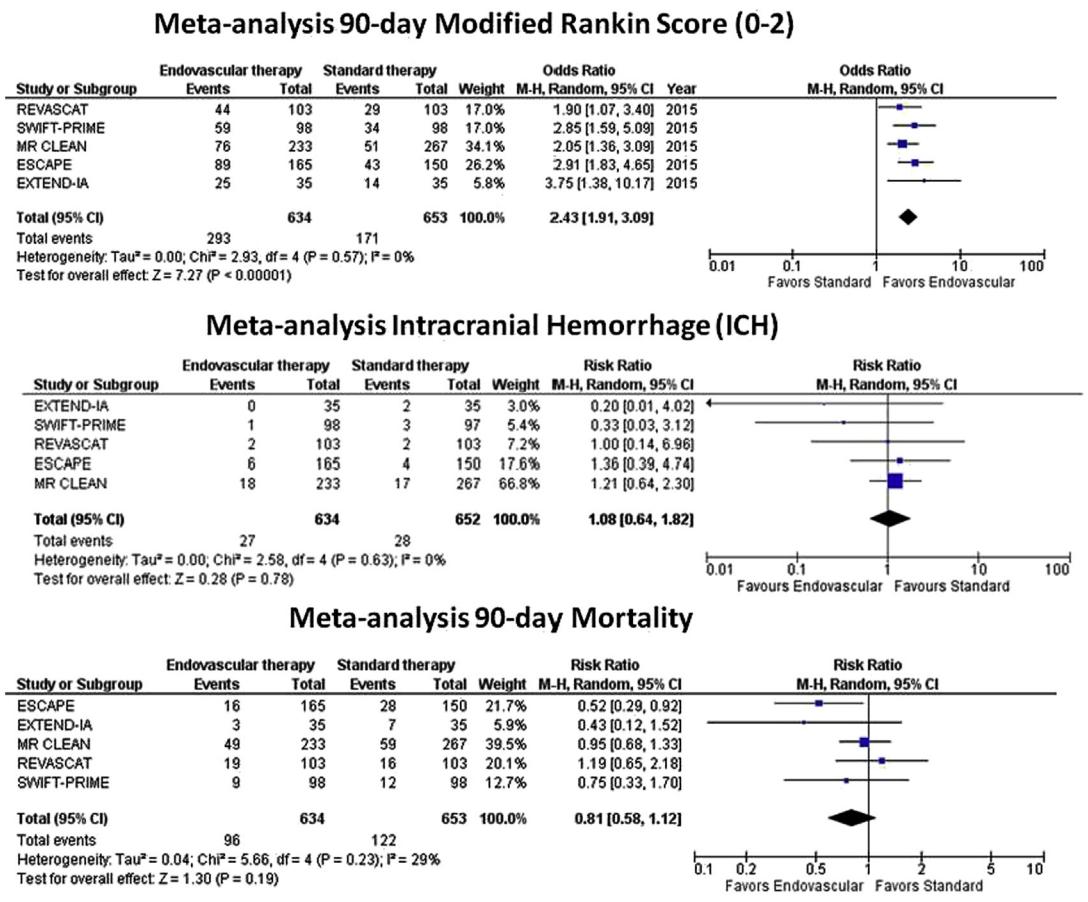
| | 90-Day Rankin 0-2 | | Symptomatic ICH | | Mortality 90 days | |
|---|---|---|---|---|---|---|
| Study Name, Year | Intervention | Control | Intervention | Control | Intervention | Control |
| MR CLEAN, 2015 | 32.6 | 19.1 | 7.7 | 6.4 | 21.0 | 22.0 |
| SWIFT-PRIME,2015 | 60.0 | 35.0 | 0.0 | 3.0 | 9.0 | 12.0 |
| EXTEND-IA, 2015 | 71.0 | 40.0 | 0.0 | 6.0 | 9.0 | 20.0 |
| ESCAPE, 2015 | 53.0 | 29.0 | 3.6 | 2.7 | 10.4 | 19.0 |
| REVASCAT, 2015 | 43.7% | 28.2 | 1.9 | 1.9 | 18.4 | 15.5 |

Values are %.
ICH = intracranial hemorrhage; other abbreviations as in Table 1.

early diffusion-weighted imaging lesion growth, and demonstrate improved outcomes after endovascular treatment (19).

The aforementioned findings are in stark contrast to the 3 previous reported studies in 2013 (20–22) that had failed to demonstrate a similar benefit. Several characteristics of the previous studies have been proposed for this discrepancy: 1) prolonged onset-to-treatment times; 2) low recanalization rates; 3) insufficient confirmation of initial arterial occlusion

**FIGURE 2 Forest Plot Meta-Analysis**




Forest plot meta-analysis of the 5 RCTs on the frequency of 90-day modified Rankin Score 0 to 2, intracranial bleeding, and 90-day mortality.
CI = confidence interval; M-H = Mantel-Haenszel test; RCT = randomized controlled trial.

in a significant percentage of patients; and 4) limited use of current stent-retriever devices (23–25). Despite the fact that these studies were technically negative, they were, nevertheless, significant because they failed to show worsening with endovascular treatment and underscored the need for use of modern retrieving devices and confirmation of large-vessel occlusion (26).

This meta-analysis confirms that endovascular treatment is effective in the treatment of acute ischemic stroke due to large vessel occlusion in an extended time window (up to 12 h), and regardless of the use of additional neuroimaging criteria for selection, especially at earlier time points (up to 6 h). This is an important breakthrough in stroke treatment, in fact the most important breakthrough since the NINDS (National Institute of Neurological Disorders and Stroke) t-PA trial that established the use of IV thrombolysis for ischemic stroke 20 years ago (27). It is anticipated to result in major changes in health care systems and accelerate the development of centers of excellence, such as comprehensive stroke centers, that will be preferentially able to accept and treat patients with the most severe ischemic strokes (18). Several current or planned studies (such as the DAWN [Trevo and Medical Management versus Medical Management Alone in Wakeup and Late Presenting Strokes], PISTE [Pragmatic Ischaemic Stroke Thrombectomy Evaluation], THERAPY [Assess the Penumbra System in the Treatment of Acute Stroke], THRACE [Trial and Cost Effectiveness Evaluation of Intra-arterial Thrombectomy in Acute Ischemic Stroke], and THRILL [Thrombectomy in Patients Ineligible for IV tPA] studies) may provide high-level evidence for the efficacy of endovascular treatment in different patient populations and subgroups. Further advances are expected with the refinement of retrieving devices and selection criteria that may allow the time window to be extended even further, up to 15 h in the anticipated DEFUSE-3 trial, or even up to 24 h in the DAWN trial (28,29). However, we should keep in mind that the phenomenon of reperfusion injury will be a significant factor that will determine the success of endovascular treatment at later time windows. Because up to one-third of stroke patients arrive at the hospital within 8 h from stroke onset, the expansion of the time window is likely to remove a major roadblock for access to ischemic stroke treatment and improve outcomes in this significant public health problem.

**STUDY LIMITATIONS.** There was heterogeneity in the neuroimaging criteria for selection of patients: The MR CLEAN study only required confirmation of large-vessel occlusion, whereas the remaining 4 studies required selection of patients with salvageable ischemic tissue. Regardless, all 5 studies consistently required pre-treatment imaging confirmation of large-vessel occlusion, in contrast to prior RCTs. The 5 studies used different time points: Three of the studies (MR CLEAN, EXTEND-IA, and SWIFT-PRIME) treated patients up to 6 h from onset, REVASCAT up to 8 h, and ESCAPE up to 12 h. It can be said that these correspond to different stages of acute ischemic injury, and are not immediately comparable. However, the positive results provide strong evidence that endovascular treatment is effective at extended time windows (up to 6 h and potentially up to 12 h). Future analyses and studies will be required to better identify patients with salvageable tissue within the time window of 6 to 12 h from stroke onset. Only the ESCAPE trial allowed randomization of patients up to 12 h, and only 49 patients were randomized in that time window. There was a trend towards improvement with intervention, but the difference was not significant. Only 1 of the studies (MR CLEAN) was allowed to proceed to the end of enrollment. Three of studies were terminated after an unplanned interim analysis (ESCAPE, EXTEND-IA, and SWIFT PRIME), whereas the fifth one (REVASCAT) was terminated after the first planned interim analysis. Even though the interim conservative analyses demonstrated that equipoise did not longer exist, and the respective data and safety monitoring boards concluded that the studies should be discontinued, it is possible that the early termination is associated with a magnification of the apparent treatment effect (30).

## CONCLUSIONS

This meta-analysis of randomized clinical trials demonstrates significantly improved functional clinical outcomes and a favorable safety profile with stent retriever endovascular therapy compared with standard treatment alone, for the management of acute stroke due to large-vessel occlusion (consistently up to 6 h, and potentially up to 12 h), and regardless of the use of additional neuroimaging criteria for selection, especially at earlier time points (up to 6 h).

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## PERSPECTIVES

**WHAT IS KNOWN?** For acute ischemic stroke, early reperfusion has been associated with favorable outcomes. To date, intravenous thrombolysis within 4.5 h after the onset of acute stroke symptoms is the most widely accepted strategy for prompt recanalization. Catheter-based therapies have been tried in patients with acute ischemic stroke with variable recanalization and clinical outcomes; however, the best endovascular method has not yet been reliably determined.

**WHAT IS NEW?** This meta-analysis evaluating the addition of endovascular treatment of ischemic stroke related to proximal intracranial arterial occlusion to conventional therapy (including IV thrombolysis) demonstrates the efficacy of endovascular treatment with stent retrievers in improving functional outcomes and remarkable safety compared to standard therapy. Furthermore, there appears to be a trend towards overall decreased 90-day mortality.

**WHAT IS NEXT?** This is an important breakthrough in stroke treatment; in fact, the most important breakthrough since the NINDS (National Institute of Neurological Disorders and Stroke) t-PA trial that established the use of IV thrombolysis for ischemic stroke 20 years ago. It is anticipated to result in major changes in healthcare systems and accelerate the development of centers of excellence, such as comprehensive stroke centers, that will be preferentially able to accept and treat patients with the most severe ischemic strokes. Several current or planned studies may provide high-level evidence for the efficacy of endovascular treatment in different patient populations and subgroups, refinement of retrieving devices and selection criteria that may allow the time window to be extended even further.

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**KEY WORDS** endovascular stroke management, intra-arterial therapy, ischemic stroke, stent retriever

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